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VOLUME VIII NUMBER 5

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CLINICAL PROCEEDINGS

OF THE CHILDRENS HOSPITAL

13th and W Streets, Washington 9, D. C.

Vol. VIII *May 1952* No. 5

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PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF THE CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinico-pathological conferences held every other Tuesday afternoon at 1:00 P.M., and from the monthly Staff meetings.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $2.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.." The Children's Hospital, Washington, D. C. Please notify on change of address.

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Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

THE CHILDREN'S HOSPITAL OF THE DISTRICT OF COLUMBIA

NEW BUILDING COMPLETION PROJECT

The overall building program provides for the removal of the existing structures on W Street; the conversion of the west wing from private and semi-private rooms to housing space for the nurses; the remodeling of wards and dispensaries; and the construction of two new wings to contain wards and service facilities for 101 patients, making the total capacity of the hospital 245. The ward wing which will extend along 13th Street will include a basement for storage and locker rooms, administrative offices on the first floor, 4 complete ward floors and the medical library on the fifth floor. The service wing, extending from the ward unit back to the present laundry building, will also contain a large basement. The general and special diet kitchens, formula laboratory and staff dining rooms will occupy the first floor of this wing and a large operating suite will be located on the second floor with the central supply on the third floor and Occupational Therapy Department on the fourth floor. A new 10-bed Premature Unit, additional class rooms, research laboratories, and histopathologic laboratory are among the other important facilities which will be provided.

The Nursing Education Department with lecture classroom, demonstration room, nursing library, and office of Director of Nursing Education will occupy the front part of the West annex; in the rear of the basement, will be located the research laboratory. An auditorium will be provided with a seating capacity of 200; the seats will be graduated from the first floor to the basement where the speaker's rostrum will be located. At one side will be a holding room for patients to be demonstrated at conferences. A projection booth and a roll-up stationary screen are additional features of the auditorium.

The following rooms will be air conditioned: pharmacy, formula laboratory, operating suite, the morgue, central supply, and the premature nursery.

These changes represent the first steps in the new plan for Children's Hospital. The buildings described above are designed to fit into a broad plan which envisages eventually complete replacement of all outmoded structures with well equipped facilities in which to expand the important medical services, teaching and research programs so necessary to the proper functioning of modern hospitals.

FEBRILE CONVULSIONS IN CHILDHOOD

A Statistical Analysis of the Clinical Features in 455 Cases

Special Report No. 230

Reginaldo Pascual, M.D.
John P. McGovern, M.D.

The purpose of this study was to more clearly define the symptom-complex, febrile convulsion, by the statistical analysis of the measurable clinical data in a large group of subjects from a decidedly heterogeneous population. Also, it was hoped that several new correlations of significance might be made.

We define a febrile convulsion as a fit, precipitated by fever of variable degree, in an individual that is conditioned by age, a potential convulsive disorder, or some unknown factors. No diseases are included in which the obvious pathology is in the meninges, brain, or spinal cord.

Data was collected from the records of 455 patients with febrile convulsions, admitted consecutively to The Children's Hospital during the six-year period, 1945 to 1950. During this period, 48,503 patients were admitted to the hospital, of which our subjects represent 0.94 per cent. This population studied is described grossly in Tables I through V. There were 252 males and 203 females with the greater proportion of white than colored patients as can be seen in Table I. Three hundred thirty of these subjects were having their first febrile convulsion, while 125 were experiencing a fit with fever for the second or multiple times.

Table II gives the number of cases by age groupings. The greatest frequency is during the second and third years of age. It was of interest to note that only 20 patients were under six months of age and that there were but four in the neonatal period.

The primary diagnoses underlying the fever in these patients and the average duration of their hospital stay are recorded in Table III. The apparent inaccuracy of there being more primary clinical diagnoses than patients with febrile convulsions is due to the fact that more than one primary clinical diagnosis was made in a considerable number of patients. Respiratory infections accounted for the distinct majority of the diagnoses. The average hospital stay of these patients was between 4 and 5 days. The average stay for the three-year period, 1945–1947, was 5.13 days, and for the period, 1948–1950, it was 4.2 days.

Rectal temperatures, when recorded at the time of convulsion, are grouped in Table IV. It is noted that the greatest number of convulsions occurred in the range of 102.2 F. to 104.0 F., but that significant numbers of subjects had seizures with temperatures above and below this range.

TABLE I

Sex and Race Incidence in 455 Patients

RACE	MALE	FEMALE
White	148	128
Colored	104	75
Total	252	203

TABLE II

Incidence by Age in 455 Patients

AGE RANGE	NUMBER OF PATIENTS
0–11 mos.	74
1–2 yrs.	194
2–3 yrs.	101
3–4 yrs.	64
4–5 yrs.	10
5 years & over	12

TABLE III

Clinical Diagnoses in Febrile Patients with Convulsions

RESPIRATORY INFECTION	CONTAGIOUS DISEASES	OTHERS
407	60	90

Average Duration of Hospital Stay

1945–47	1948–50
5.13 days	4.2 days

TABLE IV

Analysis of Cases by Temperature Range

BODY TEMPERATURE	NUMBER OF CASES
96.0–98.6	0
98.6–100.4	31
100.4–102.2	62
102.2–104.0	163
104.0–105.8	85

The duration of fever, when it was recorded, before and following the convulsive attack is indicated in Table V.

TABLE V

Duration of Fever Before and After Convulsion

TIME	FEVER PRE CONVULSION	FEVER POST CONVULSION
	No. of patients	No. of patients
1-6 min	15	—
1 hr-1 day	125	—
1-2 days	178	244
2-3 days	36	—
over 3 days	43	—
2-4 days	—	90
4-6 days	—	40
6-8 days	—	14
over 8 days	—	16

The population studied having been described, primary consideration is given to the finer correlations that could be made. These observations are tabulated in Tables VI through XII. As these tables are, for the most part, self explanatory and as they represent statistical tabulations, only brief remarks as to significance rather than lengthy descriptions are given.

The first question that we wished to answer was whether or not there is a significant difference between the number of male convulsions and female convulsions. This relationship is shown in Table VI.

TABLE VI

Comparison of Males vs Females with Convulsions

RACE	MALE	FEMALE	TOTAL
White	148	128	276 $\chi^2 = 1.45$ $P > .10$
Colored	104	75	179 $\chi^2 = 4.7$ $.05 > P > .02$
Total	252	203	455 $\chi^2 = 5.3$ $P \quad .02$

Assuming a 50-50 split between sexes, for the white patients, one gets a χ^2 (Chi square) for the observed split (148 males and 128 females) of 1.45 with an associated P (probability) greater than 0.10. Hence this data does not indicate a significant divergence from the 50-50 split. For colored subjects we have 104 males and 75 females. In this case χ^2 is 4.7 with associated P between .05 and .02 which is of borderline significance. If we compare male versus female regardless of color for a 50-50 split, χ^2 is 5.3 with the associated P between .05 and .02 which is of borderline significance only.

If one then compares white versus colored for the observed data P, is greater than .30 which would not imply any difference in distribution.

The next consideration was the possible interrelationship of sex and race with degree of temperature in febrile convulsions. For analysis, subjects were grouped above and below the mean temperature of 103.0 F. These relationships are tabulated in Tables VII and VIII.

TABLE VII

Comparison of Sex and Race vs Temperature

	<103 F.	>103 F.	TOTALS
White Male	65	56	121
White Female	41	43	84
Total	106	99	205

$\chi^2 < 1 \quad P > .3$

Testing the hypothesis that the distribution of males' temperatures was the same as for females, one obtains a χ^2 of less than 1.0 with a probability of more than .3. Thus there is no indication that there is any difference in distribution. For colored patients about the same results obtain.

TABLE VIII

Comparison of Race vs Temperature and Sex

GROUP	NO. IN GROUP	PROPORTION WITH TEMP. BELOW 103
White Male	121	.54
White Female	84	.49
Colored Male	82	.30
Colored Female	48	.35

$\chi^2 = 12.96 \quad P < .01$

A comparison of white with colored patients by temperature (again above and below 103.0 F.) and broken down by sex yields a χ^2 of about 13 and a P less than .01. (See Table VIII). The implication is that there is a marked difference colorwise in temperatures to be expected.

Note that mere inspection of the data shows a consistent color difference.

The next important consideration deals with the measurable influences upon the duration of convulsions, where duration had been recorded in the records. *A priori* for purpose of analysis and with consideration for severity of the convulsions with respect to the time element, the duration of convulsions has been divided into three groups: 1) under 5 minutes; 2) 5 minutes to 1 hour; 3) over 1 hour. The variable influences of race, sex, temperature, and family history of convulsions on duration of convulsions

are tabulated in Tables IX through XII. The duration of convulsions versus race is compared in Table IX.

TABLE IX

Comparison of Race and Duration of Convulsion

RACE	0–5 MIN.	5–60 MIN.	60 MIN.
White	57	61	16
Colored	28	53	6
Total	85	114	22

$\chi^2 = 5.27$ $.10 > P > .05$

This is a test of whether the distribution of duration of convulsions is the same for the white as for the colored patients. On the evidence of the data (P greater than .05) there cannot be concluded to be a significant difference.

Table X tests whether distribution of duration of convulsions differs by sex.

TABLE X

Comparison of Sex and Duration of Convulsion

SEX	0–5 MIN.	5–60 MIN.	60 MIN.
Male	55	56	17
Female	30	58	5
Total	85	114	22

$\chi^2 = 8.7$ $.02 > P > .01$

Since a χ^2 of the observed magnitude could occur only by chance approximately once in 100 times ($.02 > P > .01$) one suspects that there is a sex difference in distribution of duration of convulsions.

Table XI tests whether temperature is correlated with duration of convulsions.

TABLE XI

Comparison of Temperature and Duration of Convulsion

TEMPERATURE F.	0–5 MIN.	5–60 MIN.	60 MIN.
Below 103	25	38	8
Above 103	29	32	9
Total	54	70	17

$\chi^2 = .68$ $P > .50$

Since the χ^2 obtained could occur more than half of the time in random sampling ($P > .50$), there are no grounds for suspecting correlation.

Table XII is a test of whether the distribution of duration of convulsions is the same for those patients having a family history of convulsions as for those not having a family history.

TABLE XII

Comparison of Family History of Convulsion with Duration of Convulsion

FAMILY HISTORY	0-5 MIN.	5-60 MIN.	60 MIN.
Yes	4	7	3
No	80	107	18
Total	84	114	21

$\chi^2 = 2.70$ $P > .20$

Since the χ^2 obtained could have occured by chance more than once in five times ($P > .20$), one cannot say that the distributions are significantly different.

DISCUSSION

One word of caution is in order. These tests of significance have been performed on various classifications of the same data so that we have consistently ignored possible interactions in the groupings. Because of this, the inferences that are made must not be taken too literally.

As stated previously, this is an attempt only to more clearly classify the symptom-complex, febrile convulsions, from its measurable clinical components and was not designed to "cover" the whole subject of febrile convulsions. Our data could not lend itself for worthwhile analysis to the important considerations of the electroencephalographic findings and ultimate prognosis. Certain segmented studies within our group of subjects with respect to these factors are planned for the future, however.

A review of the literature failed to reveal a single large series in which the clinical characteristics of this symptom-complex were weighed by accurate analysis. For this reason, only few comparisons could be made of our data with that previously recorded. The few comparisons which could be made were only with respect to sex, age incidence and incidence in various temperature ranges. No comparative data could be found with respect to race and duration of convulsions, for example.

With deference to the preceding considerations, the following summary and conclusions may be given.

SUMMARY

1. A detailed analysis of the measurable clinical features of 455 patients with febrile convulsions is presented.

2. The greatest incidence of febrile convulsions occurs during the second

and third years. Few cases occur initially before six months or after five years of age.

3. Febrile convulsions occur more frequently in the male than in the female, but the difference is not great.

4. Respiratory infections accounted for the distinct majority of the clinical diagnoses.

5. There has been a significant reduction in the average duration of the hospital stay during the past six years.

6. The duration of fever before febrile convulsions is most usually in the range of one hour to two days.

7. The duration of fever following the convulsions is predominently in the range of one to two days.

8. The temperature range at the time of convulsion is most frequently between 102.0 F. and 104.0 F. with more temperatures lower than this, rather than higher.

9. When sex and race together are compared with the degree of temperature, no significant difference is observed.

10. When race (colored versus white) is compared with temperature, however, a real difference is seen and one may conclude that the white infant and young child, when predisposed, has a lower temperature convulsion threshold than does the colored child.

11. The duration of convulsive attacks apparently is not influenced by race.

12. The duration of convulsive attacks seems to be a function of sex.

13. A family history of convulsions apparently has no relation to the duration of the convulsion nor does the degree of temperature.

A REPORT OF A CASE OF A FUNCTIONAL ADRENAL GANGLIONEUROMA

Case Report No. 231

Harold H. Hawfield, M.D.
Gordon W. Daisley, Jr., M.D.

Ganglioneuroma is a tumor which arises from the sympathetic nervous system and is considered to be benign, even though it has malignant features in that it invades locally to the point of involving important structures making it inoperable[1, 2]. The first case of ganglioneuroma was reported in 1870 by Loretz who described a case of what now can be recognized as a mediastinal ganglioneuroma. Three types of tumors can arise from the

sympathetic nervous system; neuroblastoma, pheochromocytoma, and ganglioneuroma. There are no reported cases of pheochromoblastoma or neurocytoma although these tumors are possible[3]. Of the three types commonly seen, only the pheochromocytoma gives a clinical characteristic syndrome which makes its diagnosis pathognomonic[4]. The neuroblastomas are malignant and the initial symptoms are usually due to the metastasis that results from these tumors[5]. The ganglioneuromas, as far as can be determined from the literature, produce no characteristic clinical syndrome, but are characterized by the presence of a tumor, variable in size, which usually has existed over a long period of time[6], and cause symptoms only by virtue of their size. The case presented in this paper represents a ganglioneuroma which produced a clinical syndrome not indistinguishable from coeliac syndrome or chronic ulcerative colitis.

Stout[7] analyzed 243 cases of ganglioneuroma of the sympathetic nervous system, including in this analysis the neuroblastomas and ganglioneuromas. The tumors derived from the sympathetic nervous system can occur at any point between the base of the skull and the femoral vessels. The predominant location of the tumor was found to be in the abdomen and this occurred in 134 of the cases. Of the abdominal tumors, 31 occurred in the adrenal gland. This phenomenon is due to the fact that the medullary portion of the adrenal gland is derived from sympathetic nervous system primitive cells. Stout found in this same number of cases that the large majority of tumors occurred between the ages of 0 and 9 years (69 cases). Males and females were equally affected, and there was no difference in the occurrence of the tumor on the right or left side. It was found that the tumor was fully differentiated (ganglioneuroma) in 146 cases with no metastasis, whereas in 53 cases, there was partial differentiation (neuroblastoma) and metastasis occurred in 36 per cent.

The only positive laboratory finding which may be present is the occurrence of small calcific deposits in the tumor which are visualized by x-ray examinations[8]. These calcific deposits are due to the fact that hemorrhage occurs in the tumor and the resultant healing process brings about the deposition of calcium. It is on this basis that the preoperative diagnosis of adrenal tumor was proposed in the case to be presented. The course of the progress of the tumor may take a variable pattern[9]. The tumor, even though it is the malignant neuroblastoma may (1) undergo spontaneous hemorrhage and necrosis and disappear without any treatment other than biopsy, (2) undergo spontaneous maturation and become a ganglioneuroma which is benign[9], or (3) be treated successfully with irradiation even if local metastasis has occurred.

The surgical treatment of the tumor can be applied to both the malignant neuroblastoma and the benign ganglioneuroma depending on the

structures involved either by local involvement or metastatic involvement. Farber[10] states that there are five categories into which a patient may fall in the surgical treatment:

1. The tumor can be completely removed and have no postoperative irradiation;

2. The tumor can be biopsied with no attempt at removal and the patient given no irradiation;

3. The tumor can be partially removed because it locally involves important structures and there are no evidences of metastasis and the patient be given irradiation.

4. The tumor can be removed and a biopsy obtained from the metastasis and the patient given postoperative irradiation; or

5. A complete or incomplete removal of the tumor which was undergoing differentiation into a ganglioneuroma with or without subsequent irradiation.

The results of treatment in these sympathetic nervous system tumors has been confusing. Even though an extensive local tumor with metastasis has been found at operation, these patients can be found to be in excellent health two to four years later[11]. This can be explained on the basis that, perhaps, these tumors do undergo further differentiation into ganglioneuromas which are benign or disappear by hemorrhage and necrosis.

CASE REPORT

A 13-month old white female, L. B. 50-8469, was admitted to the Children's Hospital on July 16, 1950 with complaints of diarrhea of three months' duration. Her early developmental history was entirely normal until she was 10 months of age, at which time she began to have watery, foul-smelling stools. At first intermittent, they soon became constant, and were described by the mother as containing undigested food particles and black sand-like material, and occurring two or three times daily. There had been no associated vomiting or melena; she weighed twenty-two pounds just before the onset. Progressive weakness, semi-stupor, and inability to hold her head up prompted the mother to seek hospitalization.

Further questioning revealed that the mother had sought medical aid two months before, when the diarrhea became constant, and she noticed a protuberant abdomen and thinning of the arms and legs developing. Elimination diets had had no effect on the character of the loose stools, and stool examinations for parasites had been fruitless. Concurrently, pus had been noticed in the eyes each morning, and her upper lids drooped almost constantly except just after awakening from a nap. The child desired an increasing number of naps prior to admission, and her activity diminished markedly. There had been marked weight loss; she had had two bouts of mild upper respiratory infection in the six months before hospitalization, no other illnesses were elicited.

The details of her feeding history were as follows: She was breast fed for the first three days of life, and then switched to an evaporated milk, water, and Karo syrup formula. She spit up frequently while taking this, and at age two months, was given boiled homogenized milk, water, and Karo syrup, which she tolerated well. Boiled

whole milk was begun at six months, and after age nine months until admission she received whole milk with the exceptions noted below. She received five drops of Drisdol and the juice of one orange daily from three weeks of age, although 50 milligrams of ascorbic acid was substituted for the orange juice two months before admission. Pabena was the first solid food given, starting at five weeks of age. Pureed fruits at two months, pureed vegetables at three months, egg yolk at four months, and strained meats at five months followed, and all were tolerated well.

When the diarrhea began at age ten months, all foods were withheld for three days and only gingerale, tea, and water were given. Powdered protein milk, boiled skimmed milk, and various combinations of foods were tried in the next week without abatement of the diarrhea, and after several attempts at special non-allergic diets, the mother gradually returned to feeding her a normal diet. A rash was noted about the mouth at one time, which was attributed to soft-boiled eggs, but never recurred when hard-boiled eggs were substituted. No allergy tests were run, although allergy was strongly suspected; the father had had hay fever, and was known to be sensitive to trees and grasses.

This thin, pale, chronically ill, emaciated, little girl was lying listlessly in bed at physical examination. Her weight was sixteen pounds, fourteen ounces. The skin showed marked loss of subcutaneous tissue, and it hung in many folds. Her hair was thin, sparse, and straight; a small, soft mass near the anterior fontanelle was thought to be a sebaceous cyst. Both upper lids of the eyes appeared swollen and drooping, with conjunctival injection and a slight purulent discharge. The tongue was moist and white-coated, but there was no glossitis or geographia. The ears, nose, and throat, and chest showed no signs of infection. There was a soft, blowing, systolic murmur heard in the third left intercostal space parasternally which transmitted to the neck, and there was no thrill associated. The abdomen had the typical pot-belly appearance of a coelic, and superficial veins were prominent. Cervical, axillary, and inguinal nodes were easily palpable, probably due to the loss of tissue. The extremities were thin and showed poor muscle tone, but were not atrophied. Neurologic examination was negative.

The patient's initial work-up was directed toward establishing some disturbance or disease of the gastrointestinal tract as the cause of the diarrhea, with coeliac disease as the working impression. At the same time possible metabolic disturbances were investigated. As test after test was performed, and no light was shed on the problem, various clinical trials on therapy were tried. The foregoing are summarized below:

1. Gastrointestinal Work-up
   - A. Infectious:
     - Stool cultures for pathogens (7/17, 7/18, 7/19, 8/24) were negative.
     - Stool for ova and parasites (7/25, 8/30) were negative.
     - Complement fixation test for amebiasis (8/24) was negative.
     - Complement fixation test for leptospira (8/24) was negative.
     - Histoplasmosis skin test was negative (8/11).
   - B. Coeliac Syndrome:
     - Trypsin in stools (7/25, 7/26, 7/28) was negative, and (7/28) was positive in a 1:5 dilution.
     - Duodenal drainage (8/3) showed a normal content of trypsin.
     - Stools for fats and starches (8/16, 8/30) were normal.
   - C. Allergic:
     - Skin tests to 12 common foods were all negative.
     - On numerous differential counts of white blood cells—three eosinophils on one occasion only (9/4).
     - Clinical trials—See below

D. Roentgen:

Gastrointestinal series (8/7) was normal.

Barium enema (8/6) was normal.

Proctoscopy (8/29, 9/7) was normal; scope advance, six inches.

2. Metabolic Work-up

Carbon dioxide combining power (7/18) showed 39 volumes per cent and (9/16) 54 volumes per cent.

Blood urea nitrogen (7/17) 15 milligrams per cent.

Non-protein nitrogen (8/16) 39.5 milligrams per cent.

Plasma chlorides (7/17) 585 milligrams per cent.

Calcium (7/17) 12.7 milligrams per cent; (9/1) 12.8; (9/8) 8.5; (9/16) 10.2.

Phosphorus (7/17) 3.2 milligrams per cent; (9/8) 4.7 milligrams per cent; (9/16) 5.1 milligrams per cent.

Total proteins (7/17) 6.50 grams per cent.

Albumin 5.20 grams per cent, glubulin 1.30 grams per cent, and A/G ratio 4.1:1.

Thymol turbidity (8/11) 2.8 units.

Cephalin flocculation (8/11) 0 units at 24 hours and 2+ units at 48 hours.

Cholesterol (8/16) 160 milligrams per cent.

Sodium (8/15) 313 milligrams; (9/16) 294 milligrams per cent.

Serum lipase (8/16) 0.05 cubic centimeters of N/20 NaOH/1 cubic centimeter (normal).

Serum amylase (8/18) 30 milligrams of glucose/10 cubic centimeters (normal).

Glucose Tolerance Test:

	(8/14)	(9/1)
Fasting	100 mgm. per cent	110 mgm. per cent
½ Hr.	195 mgm. per cent	215
1 Hr.	340	220
2 Hrs.	125	120
3 Hrs.	105	80

Alkaline phosphatase (9/8) 4 Bodansky units.

Eosinophil counts (8/15) 321 cubic centimeters; (8/22) 162; 150; 102; and (8/23) 72; 51.

3. Clinical Trials

Elimination diets—starvation, goat's milk, nutramigen, denatured diets, coeliac diet, pancreatic granules (tried for various periods of time during entire hospital stay)—no effect on diarrhea.

Antibiotic—chloromycetin, kaopectate and thyroid extract (8-12 to 8-19) no effect on diarrhea.

Addition of concentrated vitamins, iron, liver extract, and B_{12}. No effect on diarrhea.

Prostigmine—(7-17 to 7-19) No effect on lid drooping or lassitude.

4. Miscellaneous Work-up

Complete blood counts and urinalyses were always within normal limits.

PPD #1 and 2—Negative.

V. P. C. (7/17) 39 centimeters.

Bone marrow (8/19) was normal.

Stools for occult blood (7/22, 8/29) were negative.

Spinal fluid examination (8/18) normal.

Chest x-ray (7/16) normal, as was the skeletal survey (7/16).

Intravenous pyelogram (8/12) showed a normal urinary tract.

At this examination, however, the x-ray films of the gastrointestinal tract series (8/7) were reviewed and the following reading was added: "A review of this and all other films shows an area of speckled calcification about one inch in diameter in the right vertebral gutter between the tenth and eleventh thoracic vertebrae. The nature of this lesion is not known. A calcified cyst, adrenal tumor, and teratoma should not be ruled out."

FIG. 1. X-ray has been retouched to show the speckled appearance in the region of the right adrenal gland (T-12). The small radio-opaque flecks seen throughout the abdomen represent barium ingested for a G. I. series.

Flat plates of the abdomen (8/17, 8/29) confirmation of speckled calcification.

From the galaxy of laboratory data presented above, it is obvious that this case baffled those connected with it. Thorough investigations of the possibilities of infection, coelic disease, mucoviscidosis, and allergy as the cause of the diarrhea showed no laboratory evidence to support any of these as the diagnosis. As the diarrhea continued unabated during the hospital course (even during a three-day period when three drams of kaopectate were given every four hours), clinical trials at treat-

ment for these diseases were tried; failure to respond only bore out the laboratory findings. The numerous blood chemistries were all within normal limits. Proctoscopic examination performed on two separate occasions revealed a normal mucosa.

The first positive finding was noted on August 12, 1950, when the speckled calcification in the adrenal region was seen on x-ray examination. Investigation of this mass prompted the intravenous pyelography, eosinophil tests, glucose tolerance tests, numerous calcium, and other blood chemistry determinations, and blood pressure determinations, all of which were within normal limits. Although the adrenal gland was strongly suspected of being the site of pathology, it could not be directly or indirectly incriminated; one clinical feature which became evident was frequent and sustained flushing of the face.

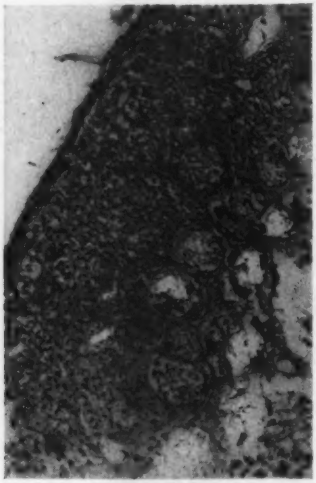

FIG. 2A

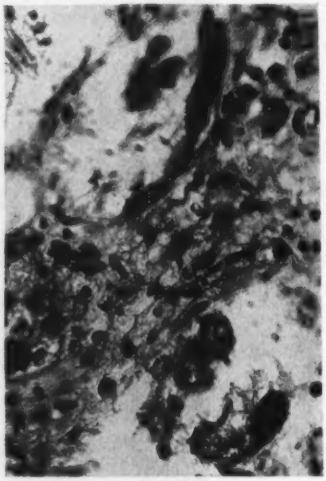

FIG. 2B

FIG. 2. A) Photomicrograph (low power) showing small peripheral area of adrenal cortex and tumor beneath.

B) Photomicrograph (high power) showing typical tumor cells.

On August 19, 1950, an eye consultation revealed that there was a duplication of the normal single row of lashes (dystichiasis) with an associated blepharoconjunctivitis and some type of dermatitis of the lids. Saline irrigations cleared the inflammation gradually, and the droopy appearance of the eyes disappeared.

The patient was sustained medically for the first 58 days of hospitalization, and in spite of all measures tried, she went downhill gradually, weighing fourteen pounds, seven ounces on September 11, 1950. The diarrhea continued. Physicians at the hospital were faced with an undiagnosed patient in whom only one abnormality had presented itself, and no one could associate the symptoms of diarrhea with a mass in the right adrenal region. When all else had failed, it was decided to operate on the patient, and accordingly, on September 12, 1950, an exploratory laporotomy was performed.

General survey of the abdominal contents showed no abnormality. In the region of the right adrenal gland there was a nodular, firm, rubbery tumor, measuring approximately 4 x 3 x 2 centimeters, which appeared to have a thin layer of adrenal cortex encapsulating it. There was no evidence of local infiltration of the tumor and there were no regional lymph nodes. The mass was shelled out, and the child returned from the operating room in good condition. Surgeons believed they had removed a neuroblastoma.

The patient tolerated the procedure well, and on the third post-operative day a normal stool was reported. From that time on, the stools remained normal, and she was placed on a regular diet. She was discharged on the eleventh post-operative day dramatically improved, having gained two pounds, and the flushing of the face had disappeared. Microscopic sections of the tumor showed it to be a benign ganglioneuroma. Follow-up observations over an eighteen-month period have revealed a perfectly normal, healthy girl of average size. There has never been another diarrheal stool noted.

SUMMARY

The case which is presented in this paper is a benign ganglioneuroma which occurred in the right adrenal and, as far as can be determined, it is the first case in which a ganglioneuroma produced a clinical syndrome. It was diagnosed preoperatively by the x-ray appearance of stippling in the region of the right adrenal. The removal of the tumor, which was technically not difficult, due to its encapsulation, resulted in complete remission of all presenting symptoms. Laboratory efforts to identify an endocrine function of the tumor removed in this case failed to reveal any functional secretion. Despite this fact, the clinical improvement indicates beyond a doubt that the tumor did have an endocrine function and was responsible for the presenting signs and symptoms.

REFERENCES

1. Ladd, W. E. and Gross, R. E.: Abdominal Surgery of Infancy and Childhood; pp. 427–440, Phila: W. B. Saunders Co., 1941, Reprinted 1948.
2. Reynolds, R. P. and Cantor, M. D.: Removal of Large Retroperitoneal Lumbar Ganglioneuroma, Surgery: **20**: 571, 1946.
3. Baumgarten, E. C. and Cantor, M. D.: Pheochromocytoma, Annals of Surgery; 111–112, 1940.
4. Stout, A. P.: Ganglioneuroma of the Sympathetic Nervous System, Surgery, Gynecology and Obstetrics: **84**: 101, 1947.
5. Farber, S.: Neuroblastoma, Abstract in American Journal of Diseases of Children: **60**: 749, 1940.
6. Cushing, H. and Wolbach, S. B.: The Transformation of a Malignant Paravertebral Sympathicoblastoma into a Benign Ganglioneuroma, American Journal of Pathology: **3**: 203, 1927.
7. Chandler, F. A. and Norcross, J. R.: Sympathicoblastoma, J. A. M. A.: **114**: 112, 1940.
8. Foot, N. C.: Pathology in Surgery: pp. 436–438, Philadelphia: J. B. Lippincott Co., 1945.

CHRONIC ULCERATIVE COLITIS

Case Report No. 232

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Reginald S. Lourie, M.D.

Chronic ulcerative colitis is a disease of unknown etiology characterized by inflammatory changes in the large bowel. It usually begins in the rectum progressing towards the cecum, but occasionally may involve the terminal ileum as well. The reaction begins in the mucosa and extends towards the serosa. Ulceration with profuse discharge of pus, mucus, and blood may progress to actual perforation. As the condition becomes chronic, scarring and fibrosis shorten the bowel and transform it into a rigid, infected tube.

This is usually considered a disease of young adults, but it is not uncommon in infants and children. In the latter age group it is often a more severe process. The onset may be acute or insiduous with a fulminating or slowly progressive course. Spontaneous remissions and exacerbations are common. The highest mortality is in the first year following the onset of symptoms. Most cases of chronic ulcerative colitis have prominent psychiatric components. Complicated family or personal situations are often present.

Sigmoidoscopy and barium enema are the most valuable diagnostic aids, although the symptoms of diarrhea, tenesmus, abdominal cramps, and the passage of blood and pus per rectum leave little doubt as to the correct diagnosis.

Treatment consists of: strict dietary program with parenteral feedings if necessary, antibiotics, blood transfusions, and the temporary use of cortisone or ACTH followed by early surgical intervention if the response is not dramatic and sustained.

The risk of developing secondary carcinomatous changes in the diseased bowel is great and increases with the duration of the disease.

The following case is reported to illustrate some of the important medical, psychiatric and surgical aspects of a rather typical case of chronic ulcerative colitis occurring in a child.

CASE REPORT

This nine-year old white boy was first admitted to Children's Hospital, Washington, D. C. on September 25, 1950 for investigation of his profuse diarrhea and marked cachexia. His family history was of significance in that he had three healthy siblings and his parents appeared well adjusted and happy. His birth and early development were normal. The onset of the present illness was somewhat difficult to establish, but

in 1943, when the patient was only three years old, he began having episodes of diarrhea associated with the passage of blood and mucus per rectum. Soon thereafter, he was admitted to a local hospital because of profound anemia. There, he received an undetermined number of blood transfusions. His private physician made the diagnosis of leukemia and informed the family that his course would be progressively downhill and that no definitive treatment was indicated.

During the intervening years, he continued to have episodes of severe bloody diarrhea followed by periods of spontaneous remission. Finally, when another physician was called to see a sibling he inquired about this patient, doubted the previous diagnosis, and arranged to have the patient admitted to Children's Hospital for study.

Physical examination on admission revealed a pale, cachectic nine-year old white boy whose listlessness and withdrawn attitude were striking. His weight was 55 pounds. He showed little or no interest in his surroundings. The heart was normal; the lungs were clear except for a few bilateral inspiratory and expiratory wheezes. The abdomen was scaphoid without masses, tenderness or rigidity. Sigmoidoscopic examination revealed inflamed rectal mucosa with numerous ulcerations from which blood and pus exuded.

The initial hemoglobin was 5.5 grams with 2,900,000 red blood cells and hematocrit was 24. Urinalysis was normal except for an occasional oxylate crystal.

Two whole blood transfusions were given which raised the hemoglobin to 12.5 grams. He was discharged from the hospital as improved.

Second Admission

On November 3, 1950 he was readmitted because of the persistence of his diarrhea and a resulting anemia. His parents stated that he had continued to have approximately six bloody stools per day since discharge. Two whole blood transfusions again returned the patient's hemoglobin to normal. Two days after admission, he was discharged to be followed at home.

Third Admission

On March 5, 1951, the patient was readmitted because of continuation of the diarrhea which always became worse during periods of nervousness or emotional excitement. The hemoglobin had fallen to 6 grams with 2,400,000 red blood cells, and for the first time, evidence of nephritis was present; albuminuria of 700 milligrams per 100 milliliters and 200 red blood cells per high power field were noted in the initial urinalysis. Physical examination was essentially unchanged from the previous admissions. The diagnosis of acute glomerular nephritis was added to the previously-diagnosed state of chronic idiopathic ulcerative colitis. At this time the seriousness of the situation was well realized by all concerned, and the necessity for surgical intervention even in the presence of nephritis seemed obvious. On March 17, 1951 under local novocain and inhalation cyclopropane anesthesia, a terminal ileostomy was performed. The two limbs of the divided ileum were brought out through separate incisions. The large bowel was red, markedly thickened, and edematous. The patient tolerated the operative procedure well. The proximal ileostomy clamp was left in place for 48 hours, was then removed and gentle saline irrigations were begun. Repeated blood transfusions kept the hemoglobin at a relatively normal level. In the postoperative period, the patient's appetite was very poor. He was depressed and melancholic and because we hoped to improve his morale and wellbeing, he was started on cortisone, 50 milligrams intramuscularly every 12 hours. This was continued for five days during which time he improved considerably.

The severity of the hematuria gradually decreased. Sigmoidoscopic examination revealed the rectum to be inflamed. Numerous small to medium-sized ulcerations could be seen throughout. Barium enema showed the typical spasticity and absence of haulstral markings together with marked shortening in length of the entire colon.

The ileostomy worked satisfactorily. Plastic sheeting, attached to the abdominal wall prevented skin reaction except in the area immediately surrounding the ileostomy.

On April 20, under cyclopropane and ether anesthesia, a colectomy was performed. The terminal ileum, ascending, transverse, descending, and a portion of the sigmoid colons were resected. Because of the gravity of his condition a second procedure, a

FIG. 1. Preoperative barium enema demonstrating the "lead pipe" appearance of the colon. Haulstral markings are absent and there is narrowing of the bowel lumen. One loop of ileum is filled with barium and appears normal. (arrow)

subdiaphragmatic vagotomy, was performed in the hopes that it might improve his prognosis. To prevent gastric stasis, a pyloromyotomy was included. After the colectomy was completed, the proximal end of the remaining rectosigmoid was brought out through a small stab wound in the left lower quadrant. The patient tolerated the operative procedure well and his general condition rapidly improved. The nephritis cleared, and the urine became normal. The patient was discharged from the hospital on May 10, 1951 having soft, fairly well formed stools per ileostomy; his hemoglobin was 13 grams. At home he got along well and became cheerful and happy. His appetite became voracious and he gained weight. His family procured a small fitted ileostomy bag, and he was able to return to school. He participated in some

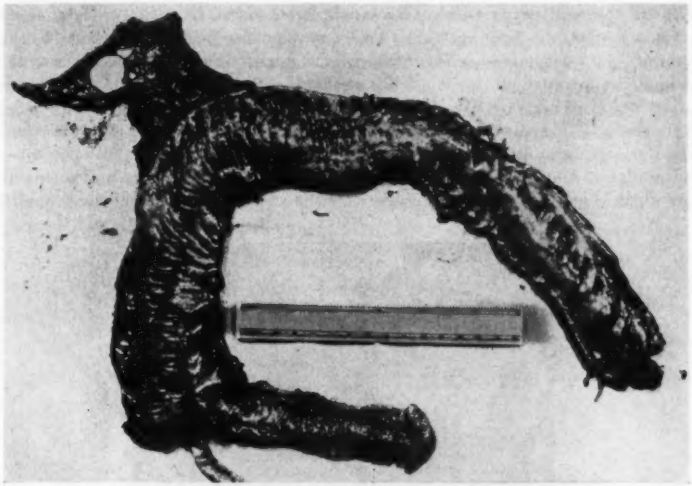

FIG. 2. Photograph of resected colon, appendix, and terminal ileum. The ulceration, scarring and shortening of the colon can be seen.

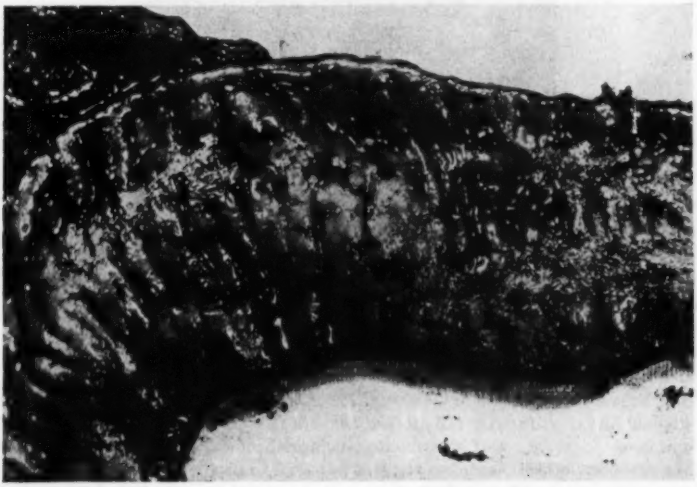

FIG. 3. Numerous small ulcers which are discharging blood and pus are demonstrated.

competitive athletics and even joined the boy scouts. His scout leader later admitted that he did not realize that the boy had ever been sick.

During the next two months, he was admitted to the hospital on three separate occasions for periods ranging from 1 to 4 days because of the complaint of crampy abdominal pain associated with vomiting. On none of these admissions was it felt that he had a mechanical intestinal obstruction; rather the desire for attention from the hospital staff appeared to be the motivating factor. Intravenous fluids, enemas and, on one occasion, gastric intubation sufficed to revert his condition to normal.

His final admission was on November 27, 1951 when he was brought into the hospital almost moribund. In the interum since his last admission he had gotten along nicely until 72 hours prior to admission when he accompanied some little friends to a

FIG. 4. Postmortem examination shows the site of perforation (arrow) and the peritonitis with dilated and adherent loops of small bowel.

double-feature western movie during which he consumed six boxes of long-stick licorice. Later that evening he began complaining of abdominal pain and by morning had become nauseated and was vomiting. The vomiting and abdominal pain continued throughout the day. Finally the mother decided that an enema should be given. Although in the past, she had given many enemas through the ileostomy using a soft rubber catheter, on this occasion she was not able to find it and instead used a hard rubber enema nozzle. She instilled one quart of unsterile soap suds and was surprised that none of the fluid was returned. He complained loudly of abdominal discomfort, but since this was not unusual during this procedure, she repeated the treatment in about six hours with the same results. When the abdominal pain, vomiting, and lassitude increased, the family physician was called and immediate hospitalization was arranged.

Physical examination at this time revealed a desperately ill, nine year old white boy who vomited fecal-like material several times during the examination. His abdomen was somewhat distended and tender throughout but no masses were palpable. A catheter, gently introduced into the ileostomy, failed to release air or fluid. A Miller-Abbott tube was inserted, attached to Wangensteen suction, and large quantities of dark, foul-smelling fluid were recovered. Intravenous fluids were administered and the patient was sedated. His condition seemed to improve somewhat and seven hours after admission he talked with the nurse on duty. However a few minutes later, when she returned to his bedside, he was dead. Vigorous resuscitative measures were instituted without avail.

FIG. 5. Another view of the traumatic perforation of ileum. The ileostomy site with surrounding skin can be seen at the top of the specimen.

Autopsy revealed a finger-tip size perforation of the bowel about 3 inches proximal to the ileostomy opening. There was a generalized peritonitis with collections of foul pus under both diaphragms, between loops of bowel, and in the pelvis. A small amount of fluid was present in both pleural cavities. The remaining rectal stump was chronically scarred but there was no active ulceration.

PSYCHIATRIC ASPECTS

Reginald S. Lourie, M.D.

The psychiatric examination of this boy and study of his family history revealed that he was a very passive child, for he was raised in an atmosphere where any show of hostility or nastiness was suppressed. He found it difficult

to know what to do with any of his normal feelings of wanting to fight or to get even. When he reached outside his home for ties to others, including children, it was difficult to make an adjustment because he had no adequate way of handling aggressive feeling on the part of these others toward him. Finally he worked out a pattern of turning his own hostile, retaliatory feelings back into himself, and the pattern of self-punishment was evident in his makeup from his pre-school days.

Another aspect that emerged in the study was the boy's feeling that he was in constant danger. This seemed to stem from his own feelings of wanting to get even with or hurt people, particularly his parents. He expected that others had these same feelings toward him and he must, therefore, be constantly on the alert. He felt it was particularly his body that could be hurt. In his search for ways of defending himself and still showing aggressive feelings, he developed means of getting people upset and angry without doing anything openly for which they could blame him. Illness became one of these devices, although he had many. However, illness soon began to take on more values than his other defenses. He found it was a way of controlling people; for instance, he could keep his mother from going off to work every day. It served the purpose of making it safe to be in contact with those whom he feared, for he felt they could not attack him in any way when he was ill. It was less necessary to deal with the problems of growing up and independent feelings, because one could be cared for and stay dependent when ill. Also he could express aggressive feelings as he needed through his illness: instead of getting angry or nasty toward people when they put pressure on him or crossed him, he would make people sorry that they had been nasty, or angry by the simple device of becoming ill. These patterns worked so well, that he had no reason to give them up, even though they were painful, progressively incapacitating methods of dealing with people. The tie between his symptoms and his relationships to people was certainly not apparent to him, or he would not have been able to use them this way and still maintain face. From this point of view, they were not consciously deliberate ways of acting and thinking.

The basis for his selection of ulcerative colitis as the means by which he accomplished these objectives is not quite clear. However, whatever its actual beginnings, it was apparent when he was first seen at nine years of age that the symptoms of his colitis were serving these other purposes, and because they were, he tended to perpetuate them as long as they accomplished these objectives and he could be more comfortable in his situation.

Separation from his environment and the lack of need to maintain his defenses there may be suspected as having a role in the remission in the hospital. An attempt was made to help the parents achieve some insight into his needs and the manner in which he was using his symptoms, in

addition to giving them some orientation in more constructive handling. Unfortunately, the boy's untimely, accidental death made it difficult to know the long-term effectiveness of this approach. However, the child did have a few months of much more comfortable total adjustment following resection of the colon.

MEDICAL ASPECTS

Marvin I. Mones, M.D.

Chronic ulcerative colitis is a progressive, chronic disease which occurs infrequently in children. Of 472 cases seen at Mayo Clinic, only 19 were in the age group of 2 to 14 years. It is characterized by remissions and exacerbations causing progressive damage to the colon. The disease process usually starts in the rectum and ascends the large bowel first producing patchy destruction in the mucosa; then fibrosis, shortening and functional dissolution of the entire large bowel occur.

Etiology

For many years, the etiology was thought to be bacterial in origin, but the specific causative agent has not been conclusively identified. Brown and Paulson observed that it was not due to endocrine, putrifactive, pancreatic or gastrogenic origin. It is not due to pellagra, the tubercle bacillus, dysentery, or sprue. B. coli and B. proteus are frequently grown from the stools. Some workers have produced temporary ulcerative lesions in the bowel by injecting bacteria into the mesenteric blood vessels. Barger's work has stimulated a great deal of interest, incriminating a diplococcus, faintly hemolytic when cultured on blood media which grew in chains of 2 to 4. He has produced lesions in animals resembling ulcerative colitis and has made a vaccine which has been successful in the treatment in his hands. All evidence as to bacteria being the cause, however, has been untenable.

Clinical studies have suggested that the inflammatory process in the colon has sensitized the area to foreign protein granulomas. Frequently, it has been observed that exacerbations of the disease process occur with acute infections of the respiratory tract. Those who have used vaccines notice increase in symptoms a few hours after injection of the autogenous material. The hypersensitive diseases, such as nephritis and rheumatic fever frequently complicate the bowel condition.

There is much evidence that allergy or hypersensitivity to food is, perhaps, causative or at least, propogative. There is usually no history of allergy in most patients and frequently the offending food is one in common use. There is no correlation between colitis, per se, and skin sensitivity tests to foods; however, by rigid elimination diets some foods may be definitely shown provocative of exacerbations of symptoms. The evaluation

of the ability of the bowel to tolerate the food can only be known by observation of the patient.

The concept of diminished lysozymes offers possibilities as an important link in the pathogenic chain which is consistent with emotional stress as an etiologic factor.

PATHOLOGY

The disease process usually begins in the rectum and extends through the large bowel. It may invade the terminal ileum, although it usually spares the remainder of the small bowel. The mucosa and submucosa become hemorrhagic and then break down to form ulcers. This progresses into the bowel wall and finally fibrosis and shortening occur. The process may continue; polyps may occur between the active ulcerated areas. Finally, perforation may result, therefore, fistulas, rectal abscess, and peritonitis may be the end result. The child may show marked lack of nutritional substance as evidenced by anemia, pellagra, peripheral neuritis, hypoproteinemia tetany, and hemorrhagic states.

Secondary changes in the physiology of the gastro-intestinal tract develop as the disease process continues. The secretory activity of the stomach is altered to the point of hypoacidity or anacidity after histimine meal. The motor and absorptive functions of the small intestine are altered.

SYMPTOMS

Ulcerative colitis may be of a severe type with symptoms of a fulminating nature and rapid downhill course. On the other hand, there is the mild type in which the patient looks well and is comfortable but has 3–4 loose bloody stools with mucus each day. The onset is usually acute. Fresh blood is first seen but later clots and tarry stools develop. The process continues with ensuing anemia, pallor, fever, weakness, exhaustion, and sometimes death. Vitamin deficiencies may develop. The disease may continue with remissions and exacerbations for years.

DIAGNOSIS

The history is of utmost importance. It will reveal the acute onset of diarrhea with mucus and blood in the stools. The proctoscopic examination will reveal the ulcerations and bleeding areas of mucosa in the early cases; with polyps and fibrosis and shortening in older cases. X-ray of the colon may be normal in early stages but later it will reveal lack of haulstrations indicating loss of pliability of the bowel, narrowing of the lumen and shortening of its length. Repeated examination of the stool for ameba and dysentery bacillus should be made and, if none are found, one can make the diagnosis of ideopathic ulcerative colitis.

TREATMENT

The accepted method of treatment, until recently, has been one of dietary restriction. A minimal bland diet is instituted when the disease is acute and supportive measures are instituted such as large doses of vitamins, correction of electrolyte imbalance, hydration, and whole blood transfusions for anemia. As the patient improves, the diet is liberalized but the patient is kept under careful surveillance. Acriflavine enemata are employed with some success.

The medical management depends on evaluation of the fundamental factors of infection, nutritional deficiencies, and disturbances of the physiology of the gastrointestinal tract. The basic diet should be calculated to give the necessary amounts of fats, carbohydrates, and protein with adequate supplement of vitamins and minerals.

Fifty patients with chronic ulcerative colitis were studied for one year by Streicher, Michael, and Kniering as to use of aureomycin as an adjunct to medical treatment. The authors felt that the majority of the group treated with aureomycin showed marked improvement. Doses of $\frac{3}{4}$ to $1\frac{1}{2}$ grams each day were employed. Proctoscopically, there was evidence of some improvement of the colon mucosa. There was marked reduction of bacterial count of the stools after institution of aureomycin therapy. The authors felt that their study should continue but no real conclusions are as yet available.

McKell and others report one case of chronic ulcerative colitis in a woman with excellent response to cortisone therapy. The improvement became apparent 48 hours after cortisone was started and preceded by one week any significant improvement in the physical appearance of the colon as seen by proctoscopic examinations. Much is said about the cortisone opening up the patient's protective shell so that psychotherapy may be employed effectively. More cases will have to be studied for proper evaluation.

Bercovitz studied twenty-two cases of ulcerative colitis who were treated with hydrosulfasol. The medication was given by rectal instillation of 1:1 or 1:3 solution in tepid tap water. These patients all had some improvement proctoscopically and clinically. He feels it is a worthwhile adjunct to general medical treatment.

Plummer, Burke, and Williams studied the effect of Banthine on chronic ulcerative colitis patients who had abdominal cramps. "Four out of five patients with abdominal cramps obtained relief on a relatively high dosage (150–200 milligrams) which had been resistant to other drugs except narcotics. The stools were unaffected as far as character and frequency."

Elliott, Keefer, and Hurxthal observed 28 cases of chronic ulcerative colitis treated with ACTH. Their conclusions were "The best results were obtained in patients with disease of short term duration and with limited

and early organic bowel changes, but with severe systemic effects of the disease."

SURGICAL ASPECTS

Marshall C. Sanford, M.D.

Today, surgery plays a more important role in the treatment of ulcerative colitis than ever before.[1–9] In the past, operation was delayed until the last minute, being resorted to only when all other measures failed. Because patients were almost moribund from reabsorption of the infected material and malnutrition, the mortality was quite high. Surgical advice is being sought in those patients in whom complications arise or who fail to respond or who respond poorly to adequate medical and psychiatric therapy—this represents about 25 per cent of all cases of ulcerative colitis.

Careful selection of cases for operation is mandatory, and of equal importance are the timing, staging, and type of operation to be employed. The usual indications for operation are debility resulting from failure to respond to therapy, hemorrhage, perforation or impending perforation, stricture, fistula, sinuses, and impending or actual carcinomatous degeneration.

Frobese[4] states, "Once this disease has ravaged the bowel, the bowel never reverts to normal state. Therefore, the surgical aim is to interrupt the fecal stream and irridicate the diseased bowel." For many years the only operation employed was ileostomy, but it did not produce uniformly good results. The complications of ileostomy alone have been high—Lahey[7] reported a mortality of 22 per cent. Obviously, ileostomy does not always prevent the usual complications of this disease, nor does it irradicate the threat of carcinomatous degeneration of the remaining diseased bowel.

Although ileostomy, by diverting the fecal stream, puts the colon at rest, there still remains a useless, diseased segment of bowel which allows the loss of blood, proteins, and electrolytes; which is likely to undergo carcinomatous changes and which; through reabsorption of the infected material, may cause arthritis, nephritis, or vascular thrombosis. The need for colectomy became apparent, and the procedure became: initial ileostomy followed, after a period of time, by colectomy which was usually performed in stages. Now ileostomy and total colectomy are often performed in one stage. Improvements in the techniques of ileostomy and the employment of such aids as the Rutzen bag have enabled patients with an ileostomy to lead a relatively normal life. Ravitch[8] and others recommend an anal ileostomy with preservation of the sphincters as the final step following the colectomy.

Following work by Dennis et al,[5] vagotomy has become another procedure added to the surgeon's armentarium. It is too early to tell the role it will actually play but probably it will be employed in the early stages of the disease.

In the case herein reported, delayed diagnosis allowed the disease to become chronic with the resulting cahexia. Psychiatric features were prominent but, with so early an onset, one wonders whether they are the cause or the effect. Nephritis, one of the frequent complications, was present in this case. Ileostomy was followed by some improvement, but the most striking improvement was that observed following colectomy. We had planned to remove the remaining rectal stump and to perform an anal ileostomy with sphincter preservation. The tragic accident of traumatic perforation of the ileum which led to the patient's death, prevented us from performing the final stage of what appeared to be satisfactory management of a nine year old boy with extensive chronic ulcerative colitis. Should another such case present itself for treatment, we would recommend a course similar to the one herein employed combining the joint efforts of the pediatrician, psychiatrist, and surgeon.

REFERENCES

1. Ladd, W. E. and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, W. B. Saunders Co, Philadelphia, Pa. p. 155, 1941.
2. Crile, G. Jr. and Turnbull, R. B.: Treatment of Ulcerative Colitis, Cleveland Clin. Quart. J. **18**: 239, 1951.
3. Nickel, W. F.: Ulcerative Colitis and Cicatrizing Enteritis, Indications for Surgery, Surg. Clin. N. A. P. 537 (April) 1950.
4. Frobese, A. S.: The Surgical Management of Reginal Enteritis and Ulcerative Colitis, Surg. Clin. N. A. P. 1725 (December) 1951.
5. Dennis, C.: Eddy, F. D.: Fryleman, H. M.; McCarthy, A. M. and Westover, D.: The Response to Vagotomy in Idiopathic Ulcerative Colitis and Regional Enteritis, Ann. Surg. **128**: 479, 1948.
6. Hardy, T. L. and Bulmer, E.: Ulcerative Colitis. Survey of 95 Cases, Brit. M. J. **2**: 812, 1933.
7. Lahey, F.: Complications of Ileostomy, S. Clin. N. A. **30**: 893, 1950.
8. Ravitch, M. M.: Total Colectomy for Benign Conditions with Preservation of Sphincters, Va. M. Month. **77**: 55 (February) 1950.
9. Colcock, B. P.: Surgical Treatment of Ulcerative Colitis, New Eng. J. Med. **242**: 320 (March 2) 1950.
10. Grace, W. J., Wolf, S., and Wolff, H. G.: Life Situations, Emotions, and Chronic Colitis, J. A. M. A. **142**: 1044 (April 8) 1950.
11. Weaver, F. M. and Holland, R. H.: Perforation of the Colon Following the Use of Enemas, Surg. **25**: 4, 613 (April) 1949.
12. Shands, W. C.: Dockerty, M. B., and Bargen, J. A.: Adenocarcinoma of the Large Intestine Associated with Chronic Ulcerative Colitis. Clinical and Pathological Features of 73 Cases, S. G. and O. **94**: 3, 302 (March) 1952.
13. Mackie, T. T.: Ulcerative Colitis. Am. Medical and Surgical Problem, J. Kansas Med. Soc. **50**: 473 (October) 1949.
14. Ross, W. D.: The Person with Ulcerative Colitis, Canadian Med. Assoc. J. **58**: 326 (April) 1948.
15. Streicker, M. H. and Kniering, R.: Clinical and Bacteriologic Response to Aureomycin in Patients with Chronic Ulcerative Colitis, Am. J. Digestive Diseases, **18**: 231 (August) 1951.
16. McKell, T. E.: Tuthill S. W., and Sullivan, A. J.: The Affective Response of the Patient with Chronic Ulcerative Colitis to Cortisone, Gastroenterology, **17**: 20 (January) 1951.
17. Bercovitz, Z. T.: Sulfhydrol Therapy in Chronic Ulcerative Colitis, Ann. Western Med. and Surg. **5**: 546 (June) 1951.
18. Plummer, K. Burke, J. O., and Williams, J. P.: Banzene in Peptic Ulcer and Chronic Ulcerative Colitis, South. Med. J. **44**: 801 (September) 1951.
19. Elliot, J. N.: Keefer, E. D., and Hurxthal, L. M.: The Treatment of Chronic Ulcerative Colitis with ACTH, New. Eng. J. Med. **245**: 288 (August) 1951.
20. Warren, R. and McKettrick, L. S.: Ileostomy in Ulcerative Colitis, Technique, Complications and Management, S. G. and O. **93**: 555 (November) 1951.
21. Barger: J. A. M. A. **83**: 332, 1924.
22. Brown and Paulson: Internat. Surg. 8263, 1929.
23. Brennamen's Practice of Pediatrics, W. F. Prior Co., Hagerstown, Md.
24. Mitchell-Nelson, Textbook of Pediatrics, W. B. Saunders Co., 5th Ed., Philadelphia, Pa.

FURTHER OBSERVATIONS ON HERPANGINA AND ITS RELATION TO THE COXSACKIE GROUP OF VIRUSES

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Despite giant strides in our knowledge of microbes and antimicrobes, there remain many apparently infectious diseases of childhood whose clinical nature is not clear and whose etiology is unknown. A recent stimulus to the investigation of these illnesses has been the isolation of a newly-discovered group of viruses, the Coxsackie group[1]. Here is a group of organisms, potential causes of disease, which have been recovered from a number of seemingly unrelated illnesses[2, 3, 4]. The problem posed is for the clinician, working with the laboratory scientist and epidemiologist to define the basic disease sources of these viruses. It is with this problem—the clinical and pathogenetic evaluation of pediatric disease sources of such small viruses—that the Research foundation of Children's Hospital has been concerned for the past two years.

Coxsackie is the term applied to a group of viruses first isolated by Dalldorf from two children with poliomyelitis in the town of Coxsackie, New York[1a]. The organisms, varying from 10–35 millimicrons in size, are characterized by their pathogenicity for suckling mice and may be classified pathologically into groups A and B. There are numerous strains in each group. Coxsackie viruses have been recovered from patients diagnosed as having both paralytic and non-paralytic poliomyelitis, aseptic meningitis, "summer grippe," "three-day fever," epidemic pleurodynia, and herpangina[1, 2, 3, 4]. To date the only diseases in which recovery of the viruses has been consistently of statistical significance are herpangina[3] and epidemic pleurodynia[4].

Therefore, the answer to some of the problems in the field must be supplied from a study of these diseases. Since herpangina is a common illness in children, a study centering about this disease has been the more feasible.

Herpangina is a specific infectious disease, originally described by Zahorsky in 1920, characterized by fever with vesicular or ulcerated throat lesions and chiefly affecting children[5]. Robert J. Huebner, M.D. and his associates at the National Institutes of Health first showed the probable etiological relationship of herpangina to the Coxsackie group of viruses[3a].

N. B. This study is supported by grant to the Research Foundation of Children's Hospital from the Viral and Rickettsial Section of the Division of Research and Fellowships, N. I. H., U. S. P. H. S. All viral determinations were performed by Dr. Robert Huebner and his associates from the Microbiological Institute of N. I. H.

METHODS AND MATERIAL

During the summers of 1950 and 1951, groups of patients at Children's Hospital with the following diagnoses were under clinical and laboratory observation for evidence of Coxsackie virus infection: (A) herpangina, (B) pharyngitis without typical herpangina throat lesions, (C) acute infectious gingivostomatitis, (D) appendicitis, (E) poliomyelitis. Several patients with miscellaneous illnesses were included.

These children were observed at frequent intervals either in the hospital or through the Out-Patient Department. Various combinations of the following laboratory examinations were performed: (A) complete blood count, (B) throat culture and anal culture for predominating bacterial organisms, (C) cerebrospinal fluid examination, (D) serum amylase determinations. The following specimens were submitted to the Microbiological institute of the National Institutes of Health for virus diagnosis: (A) multiple anal swab or stool specimens, (B) acute and convalescent paired sera, (C) miscellaneous throat and other tissue swab specimens on several patients.

CLINICAL AND PATHOGENETIC OBSERVATIONS

Herpangina

The clinical observations on 57 patients diagnosed as having herpangina closely resemble Zahorsky's original description of the disease. Their ages ranged from 6 months to 8 years. Twenty-nine children were 1 to 3 years of age. Twenty-nine of the patients were boys; 28, girls. There were eight pairs of siblings in the group. The monthly distribution of cases in 1951, when the investigation was well established before the peak season, showed that less than 5 per cent occurred on June, over 50 per cent in July, about 35 per cent in August and 10 per cent in September.

The onset of illness was usually sudden and accompanied by some degree of fever. Fifty cases gave a history of temperature elevation prior to the first dispensary visit. When first seen, twenty patients had an elevation from 101 to 105 degrees; eighteen from 99.7 to 101. Nineteen children were afebrile when first examined. The duration of fever averaged two days. Anorexia and dysphagia were recorded in 73 per cent of the cases. Sore throat was a complaint in 57 per cent of the cases. A history of vomiting was elicited in 38 per cent of the children. Abdominal pain (21 per cent) and headache (16 per cent) were occasionally noted. Two children presented at the hospital with convulsions.

The outstanding manifestation of the disease was the presence of characteristic throat lesions. These consisted of grey-white papulo-vesicular lesions about 1 to 2 millimeters in diameter or (their later counterpart) slightly larger ulcers. A zone of erythema surrounded the lesions in most

cases. The chief sites of distribution of the lesions were the anterior pillars of the tonsillar fauces. They were also seen—although less frequently—on the soft palate, uvula, and tonsils. As a rule, the lesions were in evidence for four to six days after the onset of illness. Generally, there was an associated diffuse pharyngeal hyperemia.

During 1951 four of the thirty-five children with herpangina were observed to have mild to moderately severe non-purulent conjunctivitis. The remainder of the physical examination was normal. No complications were observed during the relatively benign, self-limited course of the illness.

In most cases, the throat cultures and anal cultures of patients with herpangina revealed normal flora. Total white blood cell counts were under

HERPANGINA SYMPTOMS	
Fever	87% (2 days)
Anorexia-Dysphagia	73%
"Sore Throat"	57%
Vomiting	38%
Abdominal pain	21%
Headache	16%

HERPANGINA SIGNS	
Vesicle-ulcer	4–6 days
Anterior pillars	
Soft palate	
Uvula	
Tonsils	
Pharyngeal hyperemia	
Conjunctivitis	

10,000 in 53 per cent of cases tested; 20 per cent ranged from 10–15,000 and 27 per cent were over 15,000.

Because of the original association of Coxsackie viruses with poliomyelitis, cerebrospinal fluid examinations were performed on six children with herpangina and were found to be normal. Because of the reported occurrence of pancreatitis in infant mice with Coxsackie virus infection, serum amylase determinations were made on five children and were normal.

Gingivostomatitis

The only clinical condition frequently confused with herpangina was infectious gingivostomatitis. This is a common childhood ailment caused by the virus herpes simplex and associated with fever and vesicles or ulcers in the oral cavity, occasionally in the pharynx[6]. In over seventy patients

seen at Children's Hospital with this disease, its occurrence was year-round. The onset was more gradual than herpangina; the age incidence was about the same. In the distribution of lesions, the anterior pillars and pharynx were spared—although a diffuse pharyngitis fairly frequently preceded the onset of lesions. The buccal membranes were inflamed. The gingivae were hyperemic, hypertrophic, and hemorrhagic. There was frequently a fetor oris and almost always cervical lymphadenopathy. The ulcers were usually situated on the tongue, inner lips, buccal and sublingual mucosa. Several were seen also on the anterior pillars. The fever lingered for 3 to 4 days, the lesions for 8 to 12 days.

GINGIVOSTOMATITIS SYMPTOMS	
Fever	(3–4 days)
Dysphagia	
Sore mouth	
Vomiting	
Bad breath	
Bleeding gums	

GINGIVOSTOMATITIS SIGNS	
Vesicle-ulcer	(8–12 days)
Inner lips	
Tongue	
Buccal mucosa	
Sublingual mucosa	
Pharyngeal inflammation	
Gingivae hyperemic, hypertrophic, hemorrhagic	
Fetor oris	
Cervical adenopathy	

Pharyngitis, Appendicitis, Poliomyelitis

In the course of our observations, it seemed likely that the evanescent febrile pharyngitis fairly commonly seen in a summer's pediatric practice was related to herpangina. The history of this illness was very similar to that of herpangina-fever, anorexia, vomiting, sibling spread, and rapid recovery. Several such patients were included in this study.

A group of patients with appendicitis was included both because there had been a verbal report of the isolation of Coxsackie virus from appendicitis patients in Great Britain and because the abdominal pain in herpangina occasionally simulates that of early appendicitis.

Because the original isolations of Coxsackie viruses were made from patients with poliomyelitis, a group of children with poliomyelitis was included in this investigation. During the 1950–51 season, there was sugges-

tive evidence of herpangina in only one of 185 hospitalized children with poliomyelitis on whom the studies are presently complete. Coxsackie type virus was not recovered from this patient's specimens.

Virus Determinations

Virus specimens from the herpangina cases seen at Children's Hospital during 1950–51 yielded five immunologically distinct strains of a virus

TABLE I

Coxsackie Virus Recovery as of February 1, 1952

	VIRUS—1950		VIRUS—1951		VIRUS—TOTAL	
	Tested	Recovered	Tested	Recovered	Tested	Recovered
Herpangina	22	19	33	27	55	46
Herpangina Contact	9	6	13	5	22	11
Herpangina contact with illness			5	4	5	4
Herpangina contact without illness			8	1	8	1
Summer Pharyngitis	4	0	13	8	17	8
Gingivostomatitis	2	0	35	3	37	3
Gingivostomatitis with ulcers on anterior pillars			3	2	3	2
Appendicitis			13	0	13	0
Poliomyelitis	131	0	54	3?	185	
Diarrhea	50	2			50	2
Miscellaneous	1	0	21	0	22	0

TABLE II

Virus Strains Isolated from Herpangina Patients in 1950–1951

	1950	1951
H_1	3	12
H_2	10	
H_3	3	
H_4	3	1
HI Point		12
Not yet classified		2

causing myositis, loss of muscle function and death in suckling mice less than two weeks of age. These organisms are classified under group A of the Coxsackie viruses.

Of the fifty-five patients with herpangina on whom tests are complete, such a virus was recovered in 84 per cent. Seventy-four per cent of the paired sera already tested showed a significant strain-specific rise in neutralizing antibody during convalescence.

The only other group of patients with an incidence of Coxsackie virus recovery approximating this, is that of the children with "summer-sore throat." Coxsackie virus was found in eight out of seventeen such patients. Of five children who had been in contact with herpangina patients and who themselves had fever and pharyngitis but did not have typical throat lesions, four yielded Coxsackie viruses. Table I summarizes the isolations from the various groups surveyed at Children's Hospital in 1950–51. Table II enumerates the incidence of various strains isolated from patients with herpangina. The general incidence of Group A Coxsackie viruses in D. C. and Maryland in almost 1000 persons tested, was about 1 per cent during the summer of 1950.[3d]

DISCUSSION

Herpangina is a definite clinical entity which may be quite readily diagnosed. The evidence is strong that it is caused by viruses of the Coxsackie Group A. David, Leavitt, and Howitt recently published confirmatory evidence for this belief[3c].

Whether herpangina represents the only manifestation of infection with the A group of Coxsackie viruses is an interesting question. Certainly we have reason to suspect, as shown above, that many summertime cases of sore throat and short fevers of questionable etiology are also Coxsackie virus infections. They may be manifestations of the same process as herpangina without typical throat lesions.

The B group of Coxsackie viruses, which cause encephalomyelitis in suckling mice, has been associated mainly with epidemic pleurodynia[4]. Huebner has recently accumulated further evidence to show a causal relationship between this disease and the B group of viruses[4a].

Both group A and B viruses have been recovered by others from patients with poliomyelitis. Until recently, however, the total incidence of Coxsackie virus recovery from such patients has been less than 5 to 10 per cent[3d]. The significance of Melnick's late report of a 50 per cent incidence of group A Coxsackie virus recovery in a poliomyelitis epidemic requires further evaluation[7]. Coxsackie viruses were recovered from only 3 of the 185 patients with poliomyelitis presently tested at Children's Hospital in 1950–1951.

SUMMARY AND CONCLUSIONS

In a study of pediatric disease sources of Coxsackie viruses:

1. The definitive signs and symptoms of herpangina are elucidated.

2. A differential diagnosis is established between herpangina and infectious gingivostomatitis.

3. Further evidence is submitted for a causal relationship between the Coxsackie group of viruses and herpangina.

4. Laboratory evidence is not present for central nervous system or pancreatic involvement in patients with herpangina.

5. Laboratory evidence for Coxsackie virus infection is not present in a significant number of patients with poliomyelitis, gingivostomatitis, and appendicitis.

6. Suggestive evidence for Coxsackie virus infection is present in patients with "summer sore throat."

REFERENCES

1. (a) Dalldorf, G., and Sickles, G. M.: Unidentified filtrable agent isolated from feces of children with paralysis. Science **108**: 61, 1948.
   (b) Dalldorf, G., Sickles, G. M., Plager, H., and Gifford, R.: Virus recovered from feces of "poliomyelitis" patients pathogenic for suckling mice. J. Exper. Med. **89**: 567–582, 1949.
2. (a) Huebner, R. J., Armstrong, C., Beeman, E. A., and Cole, R. M.: Studies of Coxsackie viruses. J. A. M. A., **144**: 609–613, 1950.
   (b) Webb, C. H., Wolff, G., and Simpson, V.: Clinical features of summer disease (three-day fever) apparently of virus etiology. New Orleans M. & S. J. **101**: 249–256, 1948.
   (c) Webb, C. H., and Wolfe, G.: "Three-day fever", acute febrile disease of childhood (further observations). Am. J. Dis. Child. **80**: 245–253, 1950.
   (d) Sabin, A. B., and Steigman, A. J.: Poliomyelitis virus of low virulence in patients with epidemic "summer grippe or sore throat." Am. J. Hyg. **49**: 176–193, 1949.
   (e) Melnick, J. L., Ledinko, N., Kaplan, A. S., and Kraft, L. M.: Ohio strains of virus pathogenic for infant mice, simultaneous occurrence with poliomyelitis virus in patients with "summer grippe." J. Exper. Med. **91**: 185–195, 1950.
   (f) Melnick, J. L., Shaw, E. W., and Curnen, E. C.: Virus isolated from patients diagnosed as nonparalytic poliomyelitis or aseptic meningitis. Proc. Soc. Exper. Biol. & Med. **71**: 344–349, 1949.
   (g) Curnen, E. C., Shaw, E. W., and Melnick, J. L.: Disease resembling nonparalytic poliomyelitis associated with virus pathogenic for infant mice. J. A. M. A. **141**: 894–901, 1949.
   (h) Jaworski, A. A., and West, E. J.: Aseptic meningitis of new virus origin. J. A. M. A. **141**: 902–904, 1949.
3. (a) Huebner, R. J., Cole, R. M.; Beeman, E. A.; Bell, J. A., and Peers, J. H.: Herpangina, J. A. M. A. **145**: 628–633, 1951.
   (b) Parrott, R. H., Ross, S., Burke, F. G., and Rice, E. C.: Herpangina, New Eng. J. of Med., **245**: 275–280, (Aug. 23), 1951.
   (c) David, J. K., Leavitt, D., and Howitt, B. F.: Vesicular Pharyngitis, Pediatrics, Vol. 8, 672–677, 1951.
   (d) Cole, R. M., Bell, J. A., Beeman, E. A., and Huebner, R. J.: Studies of Coxsackie Viruses, Am. J. of Pub. Health, **41**: 1333–1454, 1951.
4. (a) Huebner, R. J.: Personal Communication.
   (b) Curnen, E. C.: Human Disease Associated with the Coxsackie Viruses; Bulletin of the N. Y. Academy of Med., **26**: 335 (May), 1950.
   (c) Howes, D. W.: A Virus Isolated from a Case Resembling Epidemic Pleurodynia, The Med. J. of Australia 597, (Nov. 3), 1951.
   (d) Findlay, G. M., and Howard, E. M.: "Coxsackie Viruses and Bornholm Disease," British Med. J. **1**: 1233, 1950.
   (e) Geffen, T.: Bornholm Disease, British Med. J., **1**: 1185, 1951.
   (f) Hopkins, J. H. S.: Bornholm Disease, British Med. J. **1**: 1230, 1950.
   (g) Weller, T. H., Enders, J. F., Buckingham, M., and Finn, J. J.: The Etiology of Epidemic Pleurodynia: A Study of Two Viruses Isolated from a Typical Outbreak, J. of Immunology, **15**; 337, 1950.
5. (a) Zahorsky, J.: Herpetic sore throat. South. M. J., **13**: 871, 1920.
   (b) Idem.; Herpangina (specific infectious disease). Arch. Pediat., **41**: 181–184, 1924.
6. (a) Long, P.: Herpetic pharyngitis and stomatitis, J. Clin. Investigation, **12**: 1119–1125, 1933.
   (b) Dodd, K., Johnson, L., and Buddingh, G.: Herpetic stomatitis, J. Pediat. **12**: 95–102, 1938.
   (c) Black, W. C.: Etiology of acute infectious gingivostomatitis (Vincent's stomatitis). J. Pediat. **20**: 145–160, 1942.
   (d) Scott, T. F. McN., and Steigman, A. J.: Acute infectious gingivostomatitis: etiology, epidemiology and clinical picture of common disorder caused by virus of herpes simplex. J. A. M. A. **117**: 999–1005, 1941.
7. Melnick, J. L., Kaplan, A. S., Vabin, E., Contreras, G., and Larkum, N.: An epidemic of paralytic poliomyelitis characterized by dual infection with poliomyelitis and Coxsackie viruses, J. Exper. Med. **94**: 471, 1951.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
David F. Bell, Jr., M.D.
Assisted by: Ruth Lau, M.D.
By Invitation: Dan Feriozi

Ruth Lau, M. D.

This one-month old colored male had two admissions in the Children's Hospital. The last admission was on October 3, and death occurred the following day.

The infant was delivered normally on September 2, with a birth weight of 6 pounds, 2 ounces. The labor had lasted approximately three days but there was no neonatal difficulty, cyanosis, or jaundice. After having been kept in the hospital for 5 days, both the mother and the infant were discharged on September 7. Two days later, the infant was admitted to Children's Hospital because of "anorexia." The only prominent physical finding at that time was the moderate cyanosis with periods of apnea lasting 60 seconds. The child was then placed in oxygen tent with immediate improvement. There were no further episodes of apnea or cyanosis. An X-ray of the chest was reported as negative and the blood count was within normal limits. Food had been withheld for 48 hours and the patient was supported by clyses. Thereafter, he was started on 5 per cent aqueous solution of glucose by mouth and was later given a weak evaporated milk formula. Under this regime, the child gained 15 ounces during this hospital stay. Penicillin was given prophylactically and oxygen was discontinued on September 11. The child remained afebrile throughout the remainder of this hospital admission and was discharged on September 22, without a definite diagnosis, but in an improved condition.

He did well at home except for a slight cold until the afternoon of October 3, at which time another episode of cyanosis was noticed during feeding. He was then rushed back to the hospital.

On this final admission, the physical examination revealed a well-developed colored infant in acute distress with minimal cyanosis. The skin was normal except for mild cyanosis. The fontanel was bulging with no pulsation. The sutures were separated 1.0 to 1.5 centimeters. There was marked venous distension over the head and arms. Nose and throat were normal. There was marked nuchal rigidity. Chest expansion was equal and bilateral. There were a few rales in the left lateral lung fields. Systolic murmur was heard in the mitral area. An arrhythmia was present; a rate of 160 alternated with a rate of 140. The liver was palpable 4 fingerbreadths below the right costal margin. The tip of the spleen was palpable and no other masses were felt. The extremities were normal. During the examination the patient had two episodes of tonic convulsions with opisthotonus.

The laboratory findings were: hemoglobin, 12.5; red blood cells, 4.6; and white blood cells, 8,800 with 63 per cent segmented, 1 per cent eosinophiles, and 36 per cent lymphocytes. A spinal tap was done immediately after admission revealing bloody fluid which appeared to represent the result of a non-purulent traumatic tap. A ventricular puncture obtained frankly purulent material which on culture revealed *Escherichia intermedium*. Fifty milliliters of this material was drained out and 600,000 units of penicillin was injected intraventricularly. The patient continued to have numerous tonic convulsions, first with respiratory cessation and then with opisthotonus. The patient was treated with sulfadizaine 0.5 grams, aureomycin 200 milligrams, intravenously, and aqueous penicillin 500,000 units every 2 hours without

avail. The second ventricular drainage was done 6 hours after the first one and 1,000,000 units of penicillin was replaced intraventricularly. The following morning the patient had further clonic convulsion with Cheyne-Stokes breathing. Death occurred at 9:15 A. M. on October 4.

DISCUSSION

Dan Feriozi, M.D.

This one month old colored male had a normal delivery with a birth weight of 6 lbs 2 oz. The labor was *prolonged* having lasted 3 days, but no neonatal difficulty, cyanosis or jaundice ensued. Mother with child were discharged from the hospital at the same time, after a stay of 5 days.

Two days after discharge, the infant was admitted to the Children's Hospital because of *anorexia*. The only prominent physical finding was moderate *cyanosis* with periods of *apnea* lasting 60 seconds, improved with oxygen. No further episode of apnea or cyanosis occurred.

One thinks of:

1. With prolonged labor, due to abnormal fetal position or disproportion:
   a) Intracranial hemorrhage from trauma, which would cause death within 24–48 hours.
   b) If the child lived longer than that time we think of a subdural hematoma with pressure over the cerebral hemisphere. (Retinal hemorrhage is a positive finding in subdural hematomas.)
   c) Cerebral edema during which the Moro reflex will be absent but will return as cerebral edema regresses. But if cerebral damage has been done it disappears and does not return.
   d) Hyaline membrane disease: occurring in premature infants or cesarian section babies who have precipitated amnionic fluid in the alveolar spaces after having breathed 1 hour, die within 48 hours (cf. Landing).
2. Anorexia, cyanosis, apnea, developed 2 days after discharged home from hospital with mother one thinks of:
   a) Again of Intracranial hemorrhage with pressure over the vital centers of the brain stem, but no history of high-pitched cry, muscular twitchings, convulsions, or Cheyne Stokes respirations developed.
      1) Toxemia or prematurity?
      2) Congenital lues.

      (But no note made of toxemia, prematurity or a positive serology.)
   b) Deminished space for pulmonary expansion due to diaphragmatic herniation, pleural effusion, cysts of mediastinum or lung.
   c) Lack of space for oxygen in alveoli: because of the lumens filled with solid material such as leukocytes, pneumonia, patchy areas

of atelectasis, tumor compressing the trachea or obstruction of the larynx or other malformation of the lungs with depression of the respiratory center. Pharyngeal or pulmonary infections, aspiration of mucous or gastric contents, or even aspiration of milk while feeding. (But an x-ray of the chest was reported negative and a blood count was reported "within normal limits"). This child was said to have remained afebrile during remainder of his stay after September 11. We do not know whether he was febrile before or not.

d) Tumors as the neuroblastoma are limited almost entirely to infancy and childhood. The neuroblastoma or sympathicoblastoma arise in the sympathetic nervous system and similar tumors may arise within the substance of the brain or cord (cf. Farber).

e) Anoxia in the neonatal period brings to mind certain types of the congenital heart diseases.
   1) Aortic atresia (die within 10 days, CMC* series) results in heart failure and death within a few days.
   2) Pulmonary atresia, also tricuspid atresia (die within 3.5 months).
   3) Transposition of the great vessels (7 months).
   4) Truncus arteriosis (17 months).
   5) Anomalous left coronary vessel in infancy (6 months).
   6) Endocardial sclerosis (review by John Craig).

f) "I would like to add here that with reference to the thymus, there is no pathological evidence to support the belief that pressure exerted by the thymus gland causes anoxia."

g) Poisoning with aniline dyes occasionally used by the laundry in marking diapers and shirts should be mentioned as a rare cause of cyanosis in infancy.

The child was without food for 48 hours during which time he was supported by clyses. Then he was started on 5% glucose soln. p. o. and later weak evaporated milk formula. We are told that the child gained 15 oz. during this hospital stay. Penicillin was given prophylactically, and oxygen discontinued on September 11. The child was discharged without a definite diagnosis, but in an improved condition.

While home, the child was said to have done well "except for a slight cold," until October 3 at which time another episode of cyanosis was noted during feeding, and he was returned to the hospital.

At this final admission physical examination showed:

a) Acute distress with minimal cyanosis, sutures separated 1.0 to 1.5 cm, fontanel bulging with no pulsation.
   Indicating an internal hydrocephaleus

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b) Marked venous distention over the head and arms, makes one think of venous obstruction from a mass at the base of the heart compressing the subclavian vessels, and possibly one of the above mentioned congenital heart defects.

c) Marked nuchal rigidity was noted on physical examination indicating meningeal irritation.

d) The lungs contained a few rales in the left lateral lung fields, which encourages one to think of the lung as the isolated source of infection which resulted in a hematological spread to involve the brain with resulting meningeal irritation.

e) An arrhythmia was said to be present with a rate of 160/min. alternating with a rate of 140/min. and a systolic murmur was heard in the mitral area. One must consider heart block in an infant with a heart rate of less than 60/min.

1) Of course the normal infant heart rate averages 120–140/min. and may increase to 170/min. during crying normally, and a systolic murmur at the mitral area depends on its intensity and quality for significance. As for example with a tricuspid atresia a systolic murmur may or may not be heard in spite of the underlying congenital heart malformation.

f) The liver was felt 4 finger breadths below the right costal margin, and the tip of the spleen was felt.

These findings can be physiological in the neonatal period and yet in this patient may be indicative of:

1) Congestive failure
2) Acute leukemia

However, no note was made of there being any petechiae over the skin, any pallor, nor any changes in the hemopoetic system, which rules out the latter rather conclusively. Although I have seen a child with acute leukemia at birth who died 17 days after birth in whom the first positive signs were pallor, ecchymotic areas over left ear.

g) Neurological:

The patient had two episodes of true convulsions with opisthotonus during the examination.

1) Convulsions with evidence of hydrocephaleus or microcephalus may suggest toxoplasmosis. Congenital toxoplasmosis may be transmitted transplacentally from a mother who herself has no clinical evidence of disease but who does have serologic evidence of it. Chorioretinitis is a common physical finding here. However, the blood usually shows a leucocytosis with increased number of monocytes and lymphocytes, and the protein of the spinal fluid is increased.

2) Torulosis most frequently involves the central nervous system. However, only few cases have been reported in children under 10 years of age. Symptoms of central nervous system cryptococcosus are those of meningitis or brain abscess.
3) Cerebral angiomatosis (Sturge-Weber syndrome). Clinically the condition is characterized by the presence of cutaneous hemangiomas especially of the face and forehead with an angiomatous neoplasia of the cerebral cortex. Convulsions become a part of the clinical pattern.

The laboratory findings of: 4,600,000 red blood cells; hemoglobin, 12.5 grams; 8,800 white blood cells with 63 segmented cells, 1 eosinophile, and 36 lymphocytes per 100 cells is not very helpful here. Blackfan did blood studies on normal children from birth up to 13 years of age. And as I understand it, his results for infants between 2 weeks and 3 months show: 8–9000 white blood cells; 4,000,000–4,600,000 red blood cells; hemoglobin, 70–100%; with polymorphonuclear cells 36–40, eosinophiles and basophiles, 2–3; lymphocytes, 55–52; and monocytes, 6–8 per 100 cells.

A spinal tap was bloody which was believed to represent the result of a non-purulent traumatic tap. No mention was made here of the appearance of the red blood cells as to whether they were crenated or not or whether there was any xanthachromic fluid or not. We must remember bleeding into the subarachroid space reveals bloody fluid from lumbar puncture. This was followed by a ventricular puncture which was frankly purulent and revealed *Escherichia intermedium*. It would be interesting to know the interval between the lumbar puncture and ventricular taps. As I understand it *Escherichia intermedium* is not a pathogen but in terminal conditions non-pathogenic organisms can become pathogenic, even to the formation of an abscess.

Fifty milliliters of this frankly purulent material was drained out and 600,000 units of penicillin was injected intraventricularly. The patient continued to have numerous tonic convulsions, first with respiratory cessation and then with opisthotonus. The patient was treated with sulfadiazine, 0.5 grams; aureomycin, 200 milligrams; intravenous as well as aqueous penicillin, 500,000 units every 2 hours to no avail. A second ventricular drainage was done 6 hours after the first one and 1,000,000 units of penicillin was replaced intraventricularly.

The following morning the patient had further clonic convulsions with Cheyne-Stokes breathing. Death occurred at 9:15 A. M. October 4.

With purulent meningitis in the newborn, 50 per cent are secondary to a focus of infection elsewhere as the lungs, ear, or from an infected meningocele or cephalhematoma. The colon or paracolon bacilli are common offenders. But with the bacterial invaders, a leucocytosis with a shift to the left

in the hemogram is expected unless the etiological agent is not of bacterial origin or else a toxic depression of the bone marrow exists.

The history given does not reveal any elevation of fever, leucocytes or elevation of any elements of the differential, either polymorphonuclear cells, lymphocytes, or monocytes. However, a granulomatous encephalomyelitis of infancy could fit this picture.

From the information given, I find it difficult to make a conclusive diagnosis, however, I would suggest the following in this order:

1. Internal hydrocephalus, secondary to a granulomatous encephalomyelitis with or without intracerebral toxoplasmosis.
2. Brain abscess, interventricular, *Escherichia intermedium* as a secondary contaminate.
3. Internal hydrocephalus secondarily infected.
4. Congenital heart disease, probably tricuspid atresia.
5. Possible combination of (1) and (4).

PATHOLOGIC DISCUSSION

David F. Bell, Jr., M.D.

Dr. Feriozi has given us a very excellent and complete differential diagnosis of the case presented. The main pathological findings at autopsy were limited to the brain and lungs. Two areas of subarachnoid hemorrhage, the larger measuring 30 centimeters in greatest diameter, were seen over the temporal and parietal portions of the cerebral hemispheres. On removal of the brain from the cranial cavity, the cortices of the right occipital region was ruptured and 30 milliliters of thick yellow purulent material escaped. Examination of the brain after formalin fixation, showed a large abscess in the right occipital lobe which had ruptured into the ventricular system. The aqueduct of sylvius was obstructed by yellowish gelatinous exudate, giving rise to an internal hydrocephalus. An abscess was found in the left cerebellar lobe and over the base of the brain an exudate measuring up to .4 centimeters in thickness, was seen. Postmortem culture of the material in the abscess cavity revealed *Escherichia intermedium*. Microscopic sections of the brain showed acute and chronic inflammation in the region of the abscess with some fibrosis flecks of calcium, but no evidence of granulomas.

The lungs on gross examination were firmer (than usual) and less crepitant, each lung weighing 10 grams greater than the normal weights. Microscopic examination showed edema and some intra-alveolar hemorrhage, with minimal signs of acute inflammation. Areas of atelectasis were present.

Meningitis and brain abscesses are uncommon in the neonatal period and are often due to an organism of the colon group.

We believe that *Escherichia intermedium* was the primary organism in this case, and not a secondary invader. It was recovered in both ante-mortem and in post-mortem cultures of the brain abscess. Dr. Feriozi discussed the possibility of infection by way of lumbar puncture; but, as should have been stated in the protocol, ventricular tap was done immediately after the lumbar puncture.

It is interesting to speculate on the etiology of the brain abscess. The usual routes (middle ear extension, umbilical infection with septicemia, pyelonephritis) are of doubtful significance in this case. There was a pulmonary infection present, but it did not seem to be severe on microscopic examination. The etiology, from our standpoint, remains unknown.

Another point that is also not clear is the question of how long this child had an abscess of the brain. It seems entirely possible that the abscess could have begun just before the first admission to the hospital and became quiescent during the administration of an antibiotic, and then progressed to the stage that was found on postmortem examination.

DISCUSSION

E. Clarence Rice, M.D.

While it is true that neonatal infections are not frequently seen at this hospital, they do occur with sufficient regularity to make mention of them. Infections through the umbilical cord with subsequent peritonitis and hepatitis are becoming increasingly rare. Over the years we have seen empyema in the newborn without apparent respiratory disease in the mother. During one summer there were eight neonatal deaths from multiple abscesses of the lung due to the staphylococcus, all of the infections having been acquired in the same hospital obstetrical nursery. Infections of the central nervous system have not been as uncommon as one might expect. Among these can be mentioned meningitis in twins due to the streptococcus; meningitis due to an organism of the colon bacillus group in two newborns who were delivered in the same hospital within one week of each other, and also a pneumococcus meningitis in a four day old infant, whose mother was not known to have had a respiratory infection.

So far as known this is the only newborn patient who has had a brain abscess at this hospital. Considering that the ductus arteriosus and foramen ovale do not close immediately at birth, bacteria in the circulation can be more easily carried to the arterial system through these shunts than in older infants. The infecting organism in the patient under discussion, *Escherichia intermedium*, is a normal inhabitant of the intestinal tract.

REFERENCES

1. Landing, B. F. et al: Pulmonary Hyaline Membrane in Newborn Infants, Pediat. **8**: 1 (July) 1951.
2. Farber, S.: (Personal Communication).
3. Craig, J.: Congenital Endocardial Sclerosis, Bull. Internat. Assoc. of Med. Museums, **30**: 15-67 (November) 1949.

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